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EDITORIAL

Making a Difference in Therapeutic Drug Monitoring of Antimicrobial Drugs; the Need for LC-MS/MS

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This supplement of the Journal of Applied Bioanalysis is dedicated to the use of liquid chromatography coupled to tandem mass spectrometry for measurement of antimicrobial drugs in human samples. Over the past decades a better understanding of acquired antimicrobial drug resistance and a clear relation with low drug concentrations has been established, resulting in clinicians asking for measurement of antimicrobial drugs in samples from patients not doing well on standard treatment. This more personalized treatment approach has resulted in an increase of the need for Therapeutic Drug Monitoring (TDM). TDM is personalized medicine that uses measured levels of drugs in a human matrix (blood, serum, plasma, liquor, …) to optimize drug treatment aiming at improving therapeutic outcome or reducing side effects or toxicity, or both. In other words, TDM can be regarded as a quality system surrounding pharmacotherapy for the benefit of the patient and the system. When performing TDM, usually parent drugs are measured but sometimes also metabolites when their concentration is relevant for patient care. The choice to measure either parent drug or metabolite or both depends on the relationship between drug concentration and the therapeutic outcome.

Historically, drugs were measured in biological matrices with gas-chromatography or radio-immunological methods. One of the first papers reporting the benefit of TDM was a paper by Duhme et al. [1] reporting the beneficial effects of digoxin monitoring in digoxin treated patients. A year later a paper was published on the added value of TDM of phenytoin in patients with epilepsy [2]. A few years later assays for the aminoglycosides (gentamicin, tobramycin, amikacin and kanamycin), well known drugs for their narrow therapeutic range and severe irreversible toxicity, came available and until 1990, TDM was generally restricted to the anti-epileptic drugs, theophyllin, cardiac drugs, aminoglycosides and vancomycin although some institutions also measured levels of tricyclic antidepressants and some antipsychotics. TDM has not only proven to be beneficial for patient outcome, but also turned out to be cost-effective [3,4], resulting in an increased use and appreciation of TDM. During many years, (radio-)immunoassays, gas-chromatography and high performance liquid chromatography with ultraviolet detection (HPLC-UV) methods were the major techniques that were used to determine concentrations of drugs in human serum or plasma. In contrast to chromatographic methods, immunoassays generally need no sample pre-treatment, and for automated high-throughput plat-

forms, only a limited number of antibiotic drug assays is available. Due to the nature of their technique, immunoassays are sometimes hindered by cross-reactivity, for instance with structurally similar co-administered drugs or endogenous compounds or with their metabolites. Gas-chromatography and HPLC-UV are less affected by these problems, but to overcome them, before having a reliable assay, these techniques often require an extensive development phase (choosing the right column and mobile phase for optimal separation of peaks) together with sample preparation and is therefore more labor intensive and generally regarded as costly. In addition, HPLC-UV methods often lack sensitivity, therefore needing sample clean-up and concentration steps before the actual analysis can take place. Nowadays, these analytical challenges have been overcome with the introduction of HPLC coupled to tandem mass spectrometry (LC-MS/MS), resulting in short runtimes coupled to highly specific and sensitive detection [5].

Modern TDM comprises several steps. Step 1 is the choice of the right dose. For choosing the right dose, some 'a priori' assumptions are necessary. The first is the need of a population pharmacokinetic (PPK) model representative for your patient. Individual patient characteristics such as gender, bodyweight, height, renal function and other relevant characteristics that have influence on pharmacokinetics, are fed into the PPK model resulting in an 'a priori' dose. In the second step, blood samples need to be drawn for dose individualization. To acquire as much information as possible from one or more samples, the methodology of Optimal Sampling has been developed, also called limited sampling [6,7]. From the PPK model sampling times are computed that result in the best prediction of relevant pharmacokinetic parameters leading to the least burden for the patient and the system to optimize the dose as early as possible. In the third strep, the outcomes of the drug concentrations measured on these optimal times, are fed to the PPK model and together with the patient characteristics will result in an adaptation of the dose. This circle is repeated as long as the therapy lasts with intervals based on the stability of the patient, very much comparable with any PDCA quality circle. The more unstable the patient (e.g. ICU-patients) the shorter the interval is. This process is also summarized as 'goal oriented, concentration controlled, model based, therapeutic drug monitoring', and for optimal patient care, reliable and fast assays are needed and LC-MS/MS can fill that gap for most drugs nowadays.

In this supplement issue we present both assays for antimicrobial drugs as well as an in-depth review on analytical assays. In the first manuscript the need for higher dosing of cephalosporins is clearly presented by Moorthy et al [8]. The observed high variability in drug concentrations in critically ill patients has prompted the need for TDM to monitor drug concentrations of cephalosporins, such as cefepime [9]. The review aims to assess and evaluate current literature for assays used to quantify cefepime bedside TDM.

Antiviral agents ganciclovir, acyclovir and their prodrugs are frequently used in transplant recipients or otherwise immunosuppressed patients to treat cytomegalovirus, herpes simplex virus or varicella zoster virus. Although the product insert contains information about posology of these drugs the significant variability in drug concentrations due to patient variability may pose patients at risk for underdosing [10,11]. In the second paper of this issue a multi analyte LC-MS/MS assay is presented by Märtson et al. suitable for routine TDM of these agents [12].
In the third manuscript a LC-MS/MS assay for an old drug, flucytosine, is described by Alffenaar et al. [13]. This drug is part of the combination treatment of cryptococcal meningitis, a severe opportunistic infection in patients with HIV [14]. Because of its narrow therapeutic window it is very suitable for TDM [15]. As this is an old drug, most frequently used in resource limited settings, development of modern assays has not been a priority. In the manuscript an easy to use assay is described which help others to implement the assay in their laboratory.

In the final manuscript by Mabelis et al. the hot topic of measurement of unbound antimicrobial drug concentrations is discussed [6]. A frequently used antimicrobial drug, ciprofloxacin, was subjected to paired measurement of total and unbound concentrations. This will better help to understand the impact of low plasma protein concentrations in critically ill patients on effective drug concentrations and the subsequent need to adjust the dose to reach the target concentration.

This special issue provides an overview of several relevant topics of bioanalytical applications in infectious diseases. As time is limited in case of treatment of severe infections, outcomes will only improve if diagnosis is made early, an adequate dose is selected, TDM is performed rapidly and correctly with a short turnaround time, followed by an adequate clinical follow-up [5]. The bioanalytical laboratories can therefore save patients' lives by providing a timely and accurate result to the physician. LC-MS/MS is a key technique in achieving these goals.

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